**REMARKS**

1. The Examiner is thanked for allowing claims 4, 5, 22, 28, 46, 50, 54, 57-61 and 64, and for indicating that claims 51, 52, 62, and 63 would be allowable if 51 and 52 were amended (as done above) to depend from 50. We have also addressed the objection to 50; the one to 71 is moot because 71 has been cancelled.

The Examiner is further thanked for according applicants a telephonic interview on June 9 to discuss a proposed amendment. The instant amendment differs from the proposed amendment in that claim 69 has been made dependent on 47, and new claim 72, parallelling 61-64, 67, 68, but dependent on 49, has been added.

In the interview, all claims were discussed, and the arguments presented were essentially identical to those of the present remarks.

The Examiner indicated that the proposed amendments to 47 and 49, requiring recited substitution of similar AAs, assuaged the PTO's concern regarding the more liberal % identity limitation of those claims, as well as the alleged indefiniteness of "conservative substitution".

We discussed whether it would be better to separately recite all 18 substitutions contemplated by claims 47 and 49, rather then use the condensed notation used presently.

The Examiner agreed that the meaning of the condensed notation was clear in view of P10, L19-23 and the discussion of that notation later in these remarks.

The Examiner's sole remaining concern was with claim 69, which was dependent on cancelled claim 53.

Claim 69 is parallel to claims 61-65, 67, 68, which have the following dependencies:

| Claim | Dependency |
|---|---|
| 61 | 50 |
| 62 | 51 (50) |
| 63 | 52 (50) |

| | |
|---|---|
| 64 | 54 (50) |
| 67 | 65 (51, 50) |
| 68 | 66 (52, 50) |

However, no comparable claim was dependent on 47 or 49. Hence, claim 69 has been made dependent on 47, and new claim 72, paralleling 69 et al., has been presented as a claim dependent on 49.

2. The finality of the present rejection is improper, because the indefiniteness issue concerning "conservative substitution" could have been raised previously against claims 53 and 54 which have recited "conservative substitutions" since the third preliminary amendment filed November 7, 2002.

3. The indefiniteness rejection is applied to new claims 65-68, but as noted above, prior claims 53 and 54 also recite "conservative substitutions".

Claims 53, 54, 65 and 66 have been amended to recite instead of "conservative substitutions", substitutions selected from the group consisting of

Gly/Ala,
Val/Ile/Leu,
Asp/Glu,
Asn/Gln,
Ser/Thr,
Lys/Arg, and
Phe/Tyr.

This limitation is fully supported by P10, L19-23. Please note that the recitation "Gly/Ala" means that Gly can be replaced by Ala or Ala replaced by Gly, as they form a single conservative substitution group. Likewise "Val/Ile/Leu" means that Val can be replaced by Ile or Leu, Ile by Val or Leu, or Leu by Val or Ile. There are a total of 18 possible substitutions. The substitution limitation has also been added to claims 47 and 49.

4. Claims 47, 49, 53 and 69-71 stand rejected for lack of description under 35 USC 112, para. 1. The instant amendment incorporates into claim 47 a limitation on the character of the substitutions which is similar to that previously presented in claim 53. However, it should be noted that amended claim 47 implicitly prohibits replacement of His, Lys, Met, Tyr and Pro residues.

The question is whether the fully disclosed species (the mature MAP-2 defined by positions 16 to 686 of SEQ ID NO:2) is sufficiently representative of the claimed genus. It is "representative" if persons skilled in the art would reasonably expect the other members of the claimed genus to have the same function as the disclosed species. This expectation may be based on a "known or disclosed correlation between function and structure".

In Example 14 of the Written Description Training Materials (WDTM), the PTO opined that a single species ("SE ID NO:3") would be representative of the genus defined by the claim "A protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A→B". In essence, the PTO was of the opinion that most of the sequences which were a 95% identical to SEQ ID NO:3 would have its enzymatic activity, and that those which didn't could be filtered out by virtue of the assay disclosed by applicant.

The WDTM did not address the issue of whether a less stringent percentage identity limitation, such as 85% (claim 47) or 90% (claim 49), might be acceptable.

As a result of the present amendment, a substitution limitation has been incorporated into claim 47. Thus, while claim 47 is broader than the WDTM Ex. 14 claims vis-a-vis the recited percentage identity, it is narrower in that it limits the individual substitutions to 18 of the 380 (20x19) theoretical possible substitutions.

While it is certainly possible for a single substitution, even a conservative one, to abolish activity, it nonetheless is well known in the art that proteins which are only 85% identical often have the same activity and that the substitutions recited in amended 47 are those least likely to perturb activity.

Please note that even though MASP-1, Clr and Cls are only 39-45% identical to MASP-2 (see P49, L11-13), they, like MASP-2, are serine proteases which activate C4. Thus, these more distant polypeptides satisfy the activity limitation of claim 4.

If the foregoing arguments are not considered persuasive, it is respectfully requested that the examiner consider whether incorporating the further limitation of claim 61 (essentially forbidding mutation at 157 conserved positions) would save claim 47.

5. Claims 47, 49, 53 and 69-71 are also rejected for lack of enablement.

We reiterate our position that high (85%) percentage identity creates a reasonable expectation of retained activity, especially when coupled with the new substitution limitation of amended claim 47.

The Examiner concedes that the specification identifies the active site regions necessary for serine protease activity, but points out that the regions which permit MASP-2 to recognize complement and to be influenced by mannan-binding have not been identified. While that is formally correct, it is plain that those functions are defined by structures conserved among MASP-1, MASP-2, Clr and Cls, as the four proteins share these characteristics. Figure 2 provides a complete alignment of the four proteins and identifies the positions for which they exhibit identical amino acids. These are likely to be the "great majority" of the AA positions which provide the "secondary and tertiary structural features".

Moreover, it is within ordinary skill in the art to study

the variation of the four proteins at the nominally unconserved residues. For example, MASP-2 117 is Ile, while the corresponding AAs in the other three proteins are Val (MASP-1), Leu (Clr) and Ile (Cls). This is conservative substitution per P10. On the other hand, at MASP-2 109, MASP-2 is Glu and MASP-1 is Asp, both hydrophilic, but Clr and Cls are hydrophobic Leu and Ala, respectively. Thus, the person skilled in the art would be more likely to vary 109 then 117 if the intent was to preserve activity.

Moreover, the distribution of conserved residues may be considered. Mutation in a large unconserved region like that of MASP-2 500-513 would be less likely to cause trouble than a mutation at 109 or 117.

The Examiner is also reminded that the prohibition of 112/1 is against undue experimentation. Thus, the skilled worker may take advantage of standard analytic techniques such as alanine substitution mutagenesis.

Finally, the Examiner is reminded that even if no guidance was given that might help identify the secondary and tertiary structural features, amended 47 is satisfied by a mutant which merely retains serine protease activity.

Respectfully submitted,

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